



PATENT

Case Docket No. NEREUS.2C1CP1

Date: April 6, 2004

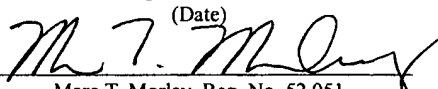
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Hayashi, et al.  
Appl. No. : 10/632,688  
Filed : August 1, 2003  
For : PHENYLHISTIN AND THE  
PHENYLHISTIN ANALOGS,  
A NEW CLASS OF ANTI-  
TUMOR COMPOUNDS  
Examiner : Unknown  
Group Art Unit : 1614

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

April 6, 2004

(Date)

  
Marc T. Morley, Reg. No. 52,051


TRANSMITTAL LETTER

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing in the above-identified application are:

- (X) A Supplemental Information Disclosure Statement.
- (X) A PTO Form 1449 listing forty-seven (47) references, which are included herewith.
- (X) Power of Attorney from Nereus Pharmaceuticals, Inc., in 2 pages, with attached copy of assignment in 2 pages.
- (X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 11-1410.
- (X) Return prepaid postcard.

  
Marc T. Morley  
Registration No. 52,051  
Attorney of Record  
Customer No. 20,995  
(619) 235-8550



## SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicant : Hayashi, et al.  
App. No. : 10/632,688  
Filed : August 1, 2003  
For : PHENYLAHISTIN AND THE  
PHENYLAHISTIN ANALOGS, A NEW  
CLASS OF ANTI-TUMOR COMPOUNDS  
Examiner : Unknown  
Group Art Unit : 1614

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Enclosed is form PTO-1449 listing 47 references that are also enclosed.

This Information Disclosure Statement is being filed before the receipt of a first Office Action on the merits, and presumably no fee is required in accordance with 37 C.F.R. § 1.97(b)(3). If a first Office Action on the merits was mailed before the mailing date of this Statement, the Commissioner is authorized to charge the fee set forth in 37 C.F.R. § 1.17(p) to Deposit Account No. 11-1410.

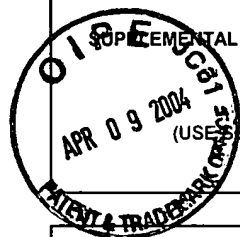
Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/6/04

By: M. T. Morley  
Marc T. Morley  
Registration No. 52,051  
Attorney of Record  
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(619) 235-8550

FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTY. DOCKET NO.  
NEREUS.2C1CP1APPLICATION NO.  
10/632,688SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT  
BY APPLICANT

(USE SEVERAL SHEETS IF NECESSARY)

APPLICANT  
Hayashi, et al.FILING DATE  
August 1, 2003GROUP  
1614

## U.S. PATENT DOCUMENTS

| EXAMINER<br>INITIAL | DOCUMENT NUMBER | DATE | NAME | CLASS | SUBCLASS | FILING DATE<br>(IF APPROPRIATE) |
|---------------------|-----------------|------|------|-------|----------|---------------------------------|
|                     |                 |      |      |       |          |                                 |
|                     |                 |      |      |       |          |                                 |

## FOREIGN PATENT DOCUMENTS

| EXAMINER<br>INITIAL |   | DOCUMENT NUMBER | DATE     | COUNTRY | CLASS | SUBCLASS | TRANSLATION     |    |
|---------------------|---|-----------------|----------|---------|-------|----------|-----------------|----|
|                     |   |                 |          |         |       |          | YES             | NO |
|                     | 1 | JP10130266      | 05/19/98 | Japan   |       |          | X<br>(Abstract) |    |

| EXAMINER<br>INITIAL | OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.) |  |
|---------------------|--|--|
|                     | 2  | Ahmed, S.A. et al. "A new rapid and simple non-radioactive assay to monitor and determine the proliferation of lymphocytes: an alternative to [ <sup>3</sup> H]thymidine incorporation assay." <i>J. Immunol. Methods</i> . 170, 211-224 (1994). |
|                     | 3  | Algaier, J. et al. "The effects of dimethyl sulfoxide on the kinetics of tubulin assembly." <i>Biochim. Biophys. Acta</i> . 954, 235-43 (1988).  |
|                     | 4  | Ali M. et al. "Toxicity of echinulin from <i>Aspergillus chevalieri</i> in rabbits." <i>Toxicology Letters</i> . 48, 235-41 (1989).  |
|                     | 5  | Bond, R., et al. "The Synthesis of Viridamine, a <i>Penicillium Viridicatum</i> Mycotoxin." <i>Synthetic Commun.</i> 19 (13&14), 2551-2566 (1989).   |
|                     | 6  | Borisy, G.G. "A Rapid Method for Quantitative Determination of Microtubule Protein using DEAE-Cellulose Filters." <i>Anal. Biochem.</i> 50, 373-385 (1972).  |
|                     | 7  | Cui, C. et al. "Novel Mammalian Cell Cycle Inhibitors, Tryprostatins A, B and Other Diketopiperazines Produced by <i>Aspergillus fumigatus</i> ." <i>J. Antibiotics</i> . 49, 534-40 (1996).   |
|                     | 8  | Cui, C. et al. "Novel Mammalian Cell Cycle Inhibitors, Tryprostatins A, B and Other Diketopiperazines Produced by <i>Aspergillus fumigatus</i> ." <i>J. Antibiotics</i> . 49, 527-33 (1996).   |
|                     | 9  | Goldani, L.Z. & Sugar, A.M. "Treatment of murine pulmonary mucormycosis with SCH 42427, a broad-spectrum triazole antifungal drug." <i>J Antimicrob Chemother.</i> 33, 369-372 (1994).   |
|                     | 10   | Gordon, D., et al. "Reductive Alkylation on a Solid Phase: Synthesis of a Piperazinedione Combinatorial Library." <i>J. Bioorg. Med. Chem. Letters</i> . 5, 47-50 (1995).  |
|                     | 11   | Hamel, E. "Antimitotic Natural Products and Their Interactions with Tubulin." <i>Med. Res. Rev.</i> 16(2), 207-31 (1996).  |
|                     | 12   | Hartwell, L.H. et al. "Checkpoints: Controls that Ensure the Order of Cell Cycle Events." <i>Science</i> . 246, 629-34 (1989).   |

EXAMINER

DATE CONSIDERED

\*EXAMINER: INITIAL IF CITATION CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP 609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED, INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

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|--|--|-----------------------------------|-------------------------------|
| FORM PTO-1449  | U.S. DEPARTMENT OF COMMERCE<br>PATENT AND TRADEMARK OFFICE | ATTY. DOCKET NO.<br>NEREUS.2C1CP1 | APPLICATION NO.<br>10/632,688 |
| SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT<br>BY APPLICANT<br><br>(USE SEVERAL SHEETS IF NECESSARY) |  | APPLICANT<br>Hayashi, et al.      |                               |
|  |  | FILING DATE<br>August 1, 2003     | GROUP<br>1614                 |

| EXAMINER<br>INITIAL | OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.) |  |
|---------------------|--|--|
|                     | 13   | Horak R.M. et al. "Structures of the Austalides A-E, Five Novel Toxic Metabolites from <i>Aspergillus ustus</i> ." <i>J.C.S. Chem. Comm.</i> 1265-67 (1981).                                       |
|                     | 14   | Iwasaki, S. "Bioactive Natural Products Interfering with Microtubule Function." <i>Kagaku to Seibutsu.</i> 32(3), 153-159 (1994).  |
|                     | 15   | Iwasaki, S. "Antimitotic Agents: Chemistry and Recognition of Tubulin Molecule." <i>Med Res Rev.</i> 13,183-198 (1993).  |
|                     | 16   | Johnson, K.A. et al. "Kinetic Analysis of Microtubule Self-assembly in Vitro." <i>J. Mol. Biol.</i> 117, 1-31 (1977).  |
|                     | 17   | Keepers Y.P., et al. "Comparison of the Sulforhodamine B Protein and Tetrazolium (MTT) Assays for in vitro Chemosensitivity Testing." <i>Eur. J. Cancer.</i> 27, 897-900 (1991).                   |
|                     | 18   | Kondoh, M. et al. "Effects of Tryprostatin Derivatives on Microtubule Assembly In Viro and In Situ." <i>J. Antibiotics.</i> 51, 801-04 (1998).   |
|                     | 19   | Krishan, A. "Rapid Flow Cytofluorometric Analysis of Mammalian Cell Cycle By Propidium Iodide Staining." <i>J. Cell Biol.</i> 66, 188-193 (1975).  |
|                     | 20   | Kupchan, S.M. et al. "Steganacin and Steganangin, Novel Antileukemic Lignan Lactones from <i>Steganotaenia araliacea</i> 1-3." <i>J. Am. Chem. Soc.</i> 95(4), 1335-36 (1973).                     |
|                     | 21   | Lacey, E. et al. "Interaction of Phomopsin A and Related Compounds with Purified Sheep Brain Tubulin." <i>Biochem. Pharmacol.</i> 36, 2133-38 (1987).  |
|                     | 22   | Laemmli, U.K. "Cleavage of Structural Proteins during the Assembly of the Head of Bacteriophage T4." <i>Nature.</i> 227, 680-85 (1970).  |
|                     | 23   | Larsen, T.O et al. "Aurantiamine, A Kiketopiperazine from Two Varieties of <i>Penicillium Aurantiogriseum</i> ." <i>Phytochemistry.</i> 31, 1613-1615 (1992).                                      |
|                     | 24   | Lee, J.C. et al. "The Reconstitution of Microtubules from Purified Calf Brain Tubulin." <i>Biochemistr.</i> 14(23), 5183-87 (1975).  |
|                     | 25   | Li, Y., et al. "Interaction of marine toxin dolastatin 10 with porcine brain tubulin: competitive inhibition of rhizoxin and phomopsin A binding." <i>Chem. Biol. Interact.</i> 93, 175-83 (1994). |
|                     | 26   | Liwo, A. et al. "Origin of the Ring-Ring Interaction in Cyclic Dipeptides Incorporating an Aromatic Amino Acid." <i>Tetrahedron Lett.</i> 26, 1873-1876 (1985).                                    |
|                     | 27   | Ludueno, R.F. "Contrasting Roles of Tau and Microtubule-associated Protein 2 in the Vinblastine-induced Aggregation of Brain Tubulin." <i>J. Biol. Chem.</i> 259:12890-98 (1984).                  |
|                     | 28   | Pettit, G.R. et al. "Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6 1a." <i>J. Med. Chem.</i> 38, 1666-1672 (1995).                                      |
|                     | 29   | Roberge, M. et al. "Antitumor Drug Fostriecin Inhibits the Mitotic Entry Checkpoint and Protein Phosphatases 1 and 2A." <i>Cancer Res.</i> 54, 6115-21 (1994).                                     |
|                     | 30   | Rowinsky, E. K. et al. "Taxol: A Novel Investigational Antimicrotubule Agent." <i>J. Natl. Cancer Inst.</i> 82, 1247-59 (1990).  |
|                     | 31   | Sackett, D.L. "Podophyllotoxin, Steganacin and Combretastatin: Natural Products that Bind at the Colchicine Site of Tubulin." <i>Pharmacol. Ther.</i> 59, 163-228 (1993).                          |

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|                     | 32   | Sherline, P., et al. "Binding of Colchicine to Purified Microtubule Protein." <i>J. Biol. Chem.</i> 250, 5481-86 (1975).  |
|                     | 33   | Smedsgaard J. et al. "Using direct electrospray mass spectrometry in taxonomy and secondary metabolite profiling of crude fungal extracts." <i>J. Microbiol. Meth.</i> 25, 5-17 (1996).   |
|                     | 34   | Steyn, P.S. "The Structures of Five Diketopiperazines from <i>Aspergillus Ustus</i> ." <i>Tetrahedron.</i> 29, 107-120 (1973).  |
|                     | 35   | Sugar, A., et al. "Comparison of Three Methods of Antifungal Susceptibility Testing with the Proposed NCCLS Standard Broth Macrodilution Assay: Lack of Effect of Phenol Red." <i>Diagn Micro and Infect Diseases.</i> 21, 129-133 (1995).                          |
|                     | 36   | Takahashi, M., et al. "Rhizoxin binding to tubulin at the maytansine-binding site." <i>Biochim. Biophys. Acta.</i> 926, 215-23 (1987).  |
|                     | 37   | Tiwari, S.C. et al. "A pH- and Temperature-Dependent Cycling Method that doubles the Yield of Microtubule Protein." <i>Anal. Biochem.</i> 215, 96-103 (1993).   |
|                     | 38   | Turner and Rodriguez. "Recent Advances in the Medicinal Chemistry of Antifungal Agents." <i>Current Pharmaceutical Design.</i> 2, 209-224 (1996).   |
|                     | 39   | Usui, T. et al. "Tryprostatin A, a specific and novel inhibitor of microtubule assembly." <i>Biochem J.</i> 333, 543-48 (1998).   |
|                     | 40   | Van der Waerden, B.L. <i>Arch Exp Pathol Pharmacol.</i> 195, 389-412, (1940).   |
|                     | 41   | Verdier-Pinard, P., et al., "Structure-Activity Analysis of the Interaction of Curacin A, the Potent Colchicine Site Antimitotic Agent, with Tubulin and Effects of Analogs on the Growth of MCF-7 breast Cancer Cells." <i>Mol. Pharmacol.</i> , 53, 62-76 (1998). |
|                     | 42   | Weisenberg, R.C. et al. "The Colchicine-Binding Protein of Mammalian Brain and its Relation to Microtubules." <i>Biochemistry</i> 7(12), 4466-79 (1968).  |
|                     | 43   | Yahara, I. et al. "Microtubule Organization of Lymphocytes and its Modulation by Patch and Cap Formation." <i>Cell.</i> 15, 251-259 (1978).   |
|                     | 44   | Yamazaki, M. et al. "Crystal Structure and Absolute Configuration of Fumitremorgin B, a Tremorgenic Toxin from <i>Aspergillus Fumigatus</i> Fres." <i>Tetrahedron Lett.</i> 1, 27-28 (1975).  |
|                     | 45   | Yamori T. <i>Jap. J. Cancer Chemother.</i> 24, 129-35 (1997).   |
|                     | 46   | Yoshida, Minoru M. <i>Protein Nucleic Acid Enzymes.</i> 38, 1753-1765 (1993).   |
|                     | 47   | Yoshimatsu, K., et al. "Mechanism of Action of E7010, an Orally Active Sulfonamide Antitumor Agent: Inhibition of Mitosis by Binding to the Colchicine Site of Tubulin." <i>Cancer Res.</i> 57, 3208-13 (1997).   |

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